5. Write the following synthesis:
   (a) Ethambutol, (b) thiacetazone, and (c) PAS.
6. Write a note on antibiotics used in tuberculosis.

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CHAPTER 17

Antifungal Agents

INTRODUCTION

Human-fungi-parasitic relationship result in mycotic illnesses. Most fungal infections (mycoses) involve superficial invasion of the skin or mucous membrane of the body orifices. These diseases can usually be controlled by local application of the antifungal agents. Fungi have different shapes and sizes. Some are large while others are minute, parasitic, and saprophytic cells. They differ from the following organisms in some important aspects:

- Algae by lack of photosynthetic ability.
- Protozoa by the lack of motility, possession of chitinuous cell wall, and ease of culture on simple media.
- Bacteria by greater size and having certain intracellular structure such as mitochondria and nuclear membrane.

CLASSIFICATION

On the basis of some differences, fungi may be classified as follows:

a. Phyco myelitis (algae-like)
b. Asco myelitis (sac-like)
c. Basidio myelitis (mushrooms)
d. Duetero myelitis

The potentially effective antifungal compounds are listed in Table 17.1.

Classification Based on the Chemical Structure, Action, and Source

The antifungal agents can be divided into the following classes, based on their chemical structure, mechanism of action, and source:

I. Antibiotics: Amphotericin B, Nystatin, Griseofulvin

II. Azoles (imidazole, triazole derivates)
Triazoles: Fluconazole, Itraconzole, Terconazole
Imidazoles: Clotrimazole, Ketoconazole, Miconazole, Bifonazole, Butoconazole, and Zinoconazole
III. Fluorinated pyrimidines: Flucytosine
IV. Chitin synthetase inhibitors: Nikomycin Z
V. Peptides/proteins: Cispentacin
VI. Miscellaneous: Ciclopirox, Tolnaftate, Naftifine, and Terbinafine

Classification Based on the Route of Administration

I. Drugs for subcutaneous and systemic mycoses: Amphotericin B, Fluconazole, Flucytosine, Itraconazole, Ketoconazole
II. Drugs for superficial mycoses: Clotrimazole, Econazole, Griseofluvin, Miconazole, Nystatin

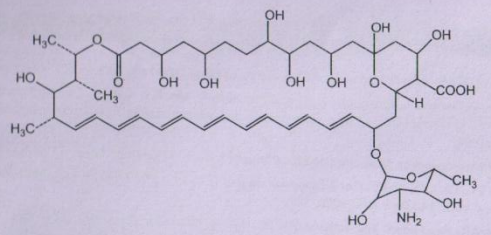
Table 17.1 Potentially effective antifungal compounds.

Disease	Compounds
Dermatophytoses	Azoles (Butoconazole, Clotrimazole, Econazole, Itraconazole, Miconazole, Oxiconazole, Sulconazole), Griseofulvin, Naftifine, Terbinafine, Tolnaftate
Aspergillosis	Amphotericin B, 5-Fluorocytosin, Itraconazole
Blastomycosis	Amphotericin B, Itraconazole, Ketoconazole
Candidiasis	Amphotercin B, 5-Fluorocytosine, Nystatin Azoles (Butaconazole, Clotrimazole, Econazole, Fluconazole, Itraconazole, Ketoconazole, Miconazole, Terconazole, Tioconazole)
Chromomycosis	5-Fluorocytosine, Itraconazole, Ketocanozole
Coccidiodomycosis	Amphotericin B, Fluconazole, Itraconazolel, Ketoconazole
Cryptococcosis	Amphotericin B, Fluconazole
Histoplasmosis	Amphrotericin B, Itraconazole, Ketoconazole
Mucormycosis	Amyphotericin B
Paracoccidioidomicosis	Itraconazole, Ketoconazole
Pneumocytosis	Trimethoprim, Sulphamethoazole, Pentamidine, Ecothionate
Pseudallescheriasis	Amphotericin B, Miconazole
Sporotrichosis	Amphotericin B, Itraconazole, Potassium iodide

SYNTHESIS AND DRUG PROFILE

I. Antibiotics

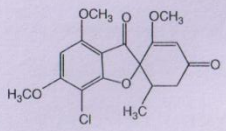
1. Amphotericin B



Mode of action: The antifungal activity of this drug depends, at least, in part, on its binding to a sterol moiety. Primarily, ergosterol that is present in the membrane of sensitive fungi, by virtue of their interaction with the sterols of cell membranes and polyenes, appear to form pores or channels. The result is an increase in the permeability of the membrane, allowing leakage of a variety of small molecules, such as intracellular potassium, magnesium, sugars, and metabolites leading to cellular death.

Properties and uses: It is polyene antibiotic obtained from *Streptomyces nodosus*. It is an amphoteric compound that consists of seven-conjugated double bond, an internal ester, a free carbonyl group, and a glycoside side chain with a primary amino group. The carbohydrate moiety is D-mycosamine. The conjugated systems are usually of all *trans* configurations, so that the ring contains a planner lipophilic segment and a less rigid hydrophilic portion. Amphotericin B is an amphoteric, forming soluble salts in both basic and acidic environments, and due to extensive unsaturation, it is unstable, primarily used as antifungal agents.

2. Griseofulvin (Fulvicin)

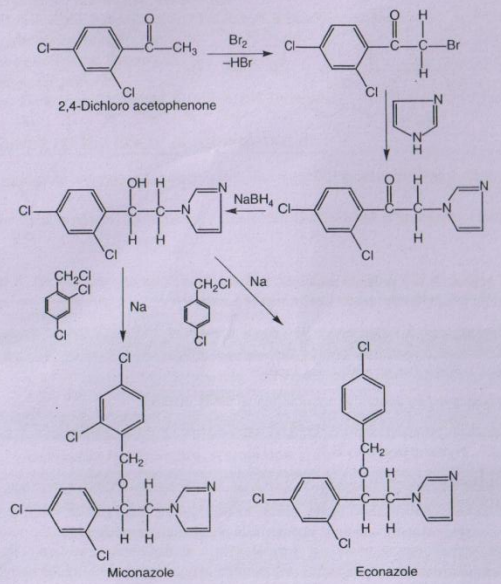


Mode of action: Griseofulvin is a fungi-static drug that causes disruption of the mitotic spindle by interacting with polymerized microtubules.

Properties and uses: Griseofulvin is a white or yellowish-white microfine powder, practically insoluble in water, freely soluble in dimethylformamide and tetrachloroethane, slightly soluble in ethanol and methanol. Used as an antifungal agent.

Synthesis

Synthesis of Miconazole and Econazole



Properties and uses of miconazole: Miconazole is a white or almost white powder, very slightly soluble in water, sparingly soluble in methanol, and slightly soluble in alcohol. It is used as an antifungal agent.

Assay: Dissolve the sample in anhydrous acetic acid, with slight heating, if necessary, and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: It is to be applied in the vagina at bedtime for seven days, and 200 mg vaginal suppositories for three days therapy.

Dosage forms: Miconazole cream I.P., B.P., Miconazole pessaries I.P., Miconazole tablets I.P., Miconazole and Hydrocortisone cream B.P., Miconazole and Hydrocortisone acetate cream B.P., Miconazole and Hydrocortisone ointment B.P.

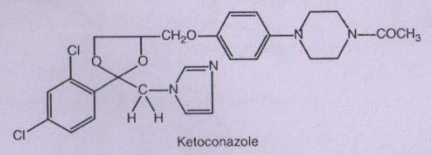
Properties and uses of econazole: Econazole is white or almost white crystalline powder, very slightly soluble in water, soluble in methanol, sparingly soluble in methylene chloride, and slightly soluble in alcohol. It is used as antifungal agent.

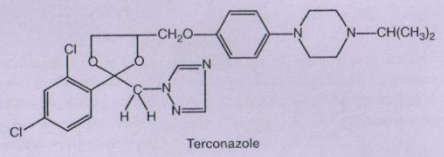
Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: It is available as a water insoluble cream (1%) to be applied twice a day.

Dosage forms: Econazole cream B.P., Econazole pessaries B.P.

2. Ketoconazole (Nizoral) **and Terconazole**





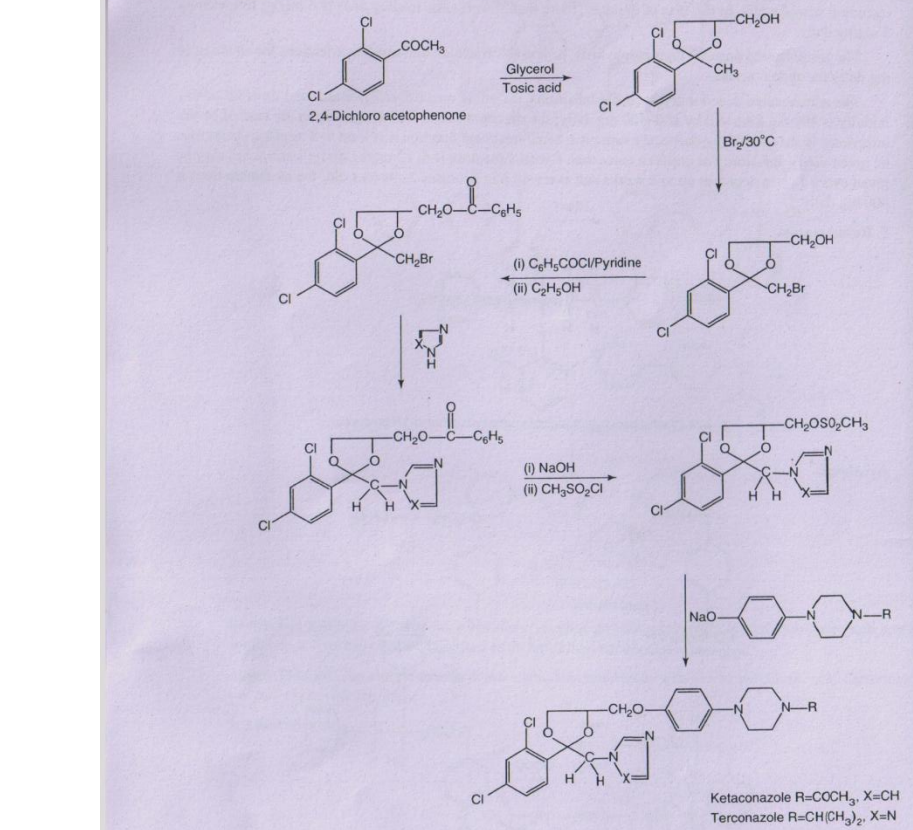
Metabolism of ketoconazole: It is extensively metabolized by deacetylase of the microsomal enzymes and all the metabolites are inactive.

Properties and uses of ketoconazole: Ketoconazole is a white powder, practically insoluble in water, soluble in methylene chloride and in methanol, sparingly soluble in alcohol. It is a racemic compound, consisting of the *cis*-2S, 4R, and *cis*-2R, 4S isomers. An investigation of the relative potencies of the four possible diastereomers of ketoconazole against rat lanosterol 1,4α-demethylase indicated that the 2S, 4R isomer was 2.5 times more active than its 2R, 4S enantiomer and the *trans* isomers, 2S, 4S, and 2R, 4R are much less active. Ketoconazole is an imidazole antifungal agent, which is a highly lipophilic compound. This property leads to high concentrations of ketoconazole in fatty tissues and purulent exudates. Ketoconazole is active against *Candida* spp. and *Cryptococcus neoformans*.

Assay of ketoconazole: Dissolve the sample in a mixture of anhydrous acetic acid and methyl ethyl ketone (1:7) and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically.

Dose: It is administered as 200 mg scored tablets and 2% topical cream.

Synthesis



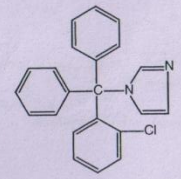
Metabolism of terconazole: It is metabolized by CYP3A4 on oral administration.

Properties and uses of terconazole: Terconazole is a white powder, practically insoluble in water, soluble in methylene chloride and in acetone, sparingly soluble in alcohol. It is a triazole derivative that is used exclusively for the control of *Vulvovaginal moniliasis* caused by *Candida albicans* and other *Candida spp*.

Assay of terconazole: Dissolve the sample in a mixture of anhydrous acetic acid and volumes of methyl ethyl ketone (1:7) and titrate with 0.1 M perchloric acid. Determine the end point potentiometrically at the second point of inflexion.

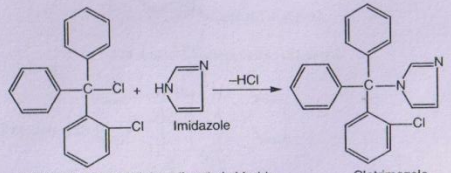
Dose: The administered dose is 80 gm vaginal suppository at bedtime for three days; and 0.4% as vaginal cream for seven days.

3. Clotrimazole



1-((2-Chlorophenyl)diphenylmethyl)-1*H*-imidazole

Synthesis



1-[(2-Chlorophenyl)diphenyl]methyl chloride — Clotrimazole

Properties and uses: Clotrimazole is a white or pale yellow crystalline powder, practically insoluble in water, soluble in alcohol and in methylene chloride. It is used as an antifungal agent.

Assay: Dissolve the sample in anhydrous acetic acid and titrate with 0.1 M perchloric acid using naphtholbenzein as indicator until the colour changes from brownish-yellow to green.

Dose: The administered dose is usually as 100 mg tablet per day at bedtime for seven days for vaginal infection.

Dosage forms: Clotrimazole cream I.P., B.P., Clotrimazole pessaries I.P., B.P.